REMARKS

Summary of Advisory Action

Claims 16-31 are pending. The Examiner has indicated that claims 21 and 26 are in condition for allowance, and that claims 16, 17, 19, 20, 22, 24, 25, 27, 28 and 30 are rejected under 35 U.S.C. § 112, first paragraph. This rejection is addressed below.

Summary of Invention

The invention features methods of screening for compounds that may be useful for the treatment of Alzheimer's Disease. These methods stem from Applicants' discovery that endocytic pathway abnormalities in sporadic Alzheimer's disease identify the disease at a very early stage and likely alter amyloid precursor protein processing.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 16, 17, 19, 20, 22, 24, 25, 27, 28 and 30 under 35 U.S.C. § 112, first paragraph, stand rejected as lacking enablement. As indicated in the Advisory Action issued on December 24, 2003, the Examiner bases this rejection on three grounds: first, that applicants' fail to enable the production of a mouse that acutely expresses the rab5 transgene; second, that the phenotype of a rab5 transgenic mouse is unpredictable; and third, that applicants' specification fails to provide guidance regarding the type of promoter to be used in producing a rab5 transgenic mouse. As an initial matter,

applicants note that they disagree with the present rejection, but have amended the claims to expedite prosecution.

The Examiner rejects claims 16 and 22, and their dependent claims, as lacking enablement for encompassing a mouse that acutely expresses a rab5 transgene. Claims 16 and 22 are now directed to *in vitro* methods of compound screening.

The Examiner rejects claims 27 and 30, and their dependent claims, for encompassing a mouse that acutely expresses a rab5 transgene. The claims now require a mouse that stably expresses a rab5 transgene. Thus, this basis for the enablement rejection should be withdrawn.

In response to the Examiner's concern, regarding whether or not the phenotype of a transgenic mouse that stably expresses rab5 is predictable, applicants note that enablement does not require absolute predictability in carrying out a claimed method. Rather, the law requires only that the specification in combination with the art provide a description that allows the claimed invention to be made and used without undue experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Applicants have clearly satisfied this requirement. Applicants have provided ample guidance regarding the generation and selection of a rab5 transgenic mouse having the desired phenotype (i.e., having increased endocytic pathway activity). In *In re Wands* the practice of the claimed invention required screening of monoclonal antibodies having the desired characteristics; enablement is not negated by the necessity for some experimentation or unpredictability, provided that experimentation is not undue. Even if

a skilled artisan were unable to choose an expression system that would allow appropriate expression with certainty, this does not negate enablement. The screening for mice having the claimed characteristics is a standard step; it is not undue experimentation.

Applicants have disclosed that murine L cells expressing rab5 *in vitro* exhibit an increase in endocytic pathway activity (page 16, line 7, to page 17, line 5). The Examiner has provided no reason to doubt that the observed phenotype of a cell stably expressing rab5 *in vitro* would fail to correlate with the predicted phenotype of a cell expressing rab5 *in vivo*. M.P.E.P. 2164.02:

> . . . the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51, F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1994) reversing the PTO decision based on finding that *in vitro* data did not support in vivo applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example.

As acknowledged by the Examiner, applicants have successfully expressed rab5 in murine cells *in vitro* and shown that this expression causes endosomal and hydrolase trafficking abnormalities reminiscent of those observed in human patients with early onset Alzheimer's disease. This cellular phenotype is predicted to correlate with the *in vivo* cellular phenotype of a transgenic mouse that stably expresses the rab5 transgene.

Moreover, using techniques available at the time of filing, applicants have successfully demonstrated that the acute expression of rab5 in murine cells *in vivo* is consistent with the cellular phenotype observed in murine cells *in vitro* (Declaration of

Dr. Nixon, submitted October 9, 2003). Regarding these experiments, the Examiner states:

> [S]ince the *in vivo* experiments described in the Declaration of January 8, 2003 were carried out using HSV to produce mice that acutely overexpress rab5 in mouse brains rather than involving the production of transgenic mice as described in the specification, *the phenotype disclosed in the Declaration would not be considered predictive of the phenotype exhibited by rab5 transgenic mice.*

The Examiner has failed to provide any evidence showing that the mode of expression, i.e., acute versus stable, would affect the predicted *in vivo* cellular phenotype. Specific technical reasons are required to support the Examiner's enablement rejection, (M.P.E.P. 2164.04).

> The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation...References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. However, specific technical reasons are always required.

The Examiner has failed to provide such reasons.

In sum, applicants submit that the rejection of the claims as unpredictable is inappropriate. Applicants have provided *in vitro* and *in vivo* data showing that rab5 transgene expression increases endocytic pathway activity in murine cells *in vitro* and *in vivo* as predicted in the application. It is not necessary that every rab5 transgenic mouse produced have increased endocytic pathway activity, rather case law requires only that undue experimentation is not required to select a mouse having the desired phenotype.

> The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. (M.P.E.P. 2164.08(b))

Using the methods disclosed in applicants' specification, one skilled in the art could reliably produce and select a rab5 transgenic mouse having an increase in the activity of an endocytic pathway. Thus, this basis for the enablement rejection should be withdrawn.

Guidance relating to rab5 transgene promoters

The Examiner asserts that applicants have failed to provide specific guidance regarding promoters that may be used to express the rab5 transgene. The promoter used to express the rab5 transgene is not a novel aspect of the invention and many promoters known in the art could be used to predictably generate an endocytic pathway phenotype. A patent need not teach and preferably omits what is well known in the art. *In re Buchner*, 929 F.2d 660,661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The generation of a rab5 transgenic mouse requires only that the rab5 transgene be expressed. A myriad of promoters capable of driving protein expression in a transgenic mouse are known in the art and no specific guidance regarding such promoters is required.

Nonetheless, contrary to the Examiner's assertion, applicants' specification discloses exemplary promoters useful in generating a transgenic mouse. For example, applicants provide at page 17, under the heading "Example 4: Transgenic mice models having endosomal and hydrolase trafficking abnormalities in AD brain," three exemplary promoters that are useful for the production of transgenic animals, such as rab5 transgenic mice. Applicants state:

> Transgenic mouse lines overexpressing any of the foregoing constructs provide useful animal models for identifying drugs useful for the treatment of AD. These mice can be made using standard techniques. If desired, the *expression of the transgenes can be restricted to neurons by use of a promoter such as the Thy1.1, neuron-specific enolase, or Tα1 α-tubulin promoters*. (page 17, lines 8-12.)

In addition, applicants describe the successful production of an exemplary transgenic mouse overexpressing the human 46-kDa mannose 6-phosphate receptor (MPR46) under the control of the thy1.1 promoter, as described at page 17, line 21, to page 19, line 4.

In sum, applicants provide exemplary promoters that are useful in generating the claimed *rab5*-expressing transgenic mice, and further provide a working example of a transgenic mouse generated using the methods described in applicants' specification. This disclosure, when coupled with information known to the skilled artisan, satisfies the enablement requirement. Thus, this basis for the rejection should also be withdrawn.

Information Disclosure Statement

Applicants note that an Information Disclosure Statement, a form PTO-1449, and references listed on the form PTO-1449 are submitted herewith. Applicants respectfully request that the Examiner initial and return the form PTO-1449.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 15, 2007

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045